CERTIFICATE OF ELECTRONIC TRANSMISSION
37 C.F.R. § 1.8

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May 7, 2007
Date

David L. Parker

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Didier Trono
Maciej Wiznerowicz

Serial No.: 10/720,987

Filed: November 24, 2003

For: COMPOSITIONS AND SYSTEMS FOR THE REGULATION OF GENES

Group Art Unit: 1635

Examiner: Vivlemore, Tracy Ann

Atty. Dkt. No.: CLFR:023US

REPLY BRIEF

MS Appeal Briefs
Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

Appellants hereby submit this Reply Brief to the Board of Patent Appeals and Interferences in response to the Examiner's Answer dated March 8, 2007, making May 8, 2007 the due date.

Enclosed herewith is a request for oral argument, along with the appropriate fee. Should such request or fee be deficient or absent, consider this paragraph such a request and authorization to withdraw the appropriate fee under 37 C.F.R. §§ 1.16 to 1.21 from Fulbright & Jaworski L.L.P. Account No.: 50-1212/CLFR:023US.

The only two rejections remaining are i) an obviousness rejection of all of the appealed claims (claims 1-7, 9-11, 13, 41 and 46-47) over Giordano, Elbasher (EMBO), Elabashir (Nature), Deuschle and Verma, and ii) a rejection of the mammalian cell claims 41, 46 and 47 on the basis of 35 U.S.C. §101.

i) Obviousness Rejection

Appellants would first like to put this rejection, and Appellant's argument, in context: it is particularly telling that the Examiner has found it necessary to combine 5 different references in an attempt to put together all of the pieces of the pending obviousness rejection – and still the rejection falls short. The elements of the main claim are a polynucleotide construct comprising an ***siRNA coding region*** linked to an ***externally controllable RNA polymerase III promoter***, wherein the expression of the siRNA is regulated by a polypeptide regulator ***having both a DNA binding domain and a repressor domain***. Here is a short-hand denotation of what Appellants understand the references are being cited for, and their shortcomings:

Giordano: for the proposition that it teaches an siRNA linked to an externally controllable RNA polymerase III promoter. However, Giordano admittedly fails to teach a polypeptide regulator having ***both*** a DNA binding domain and a repressor domain. In fact, it teaches to instead use a regulator having only a DNA binding domain. (col. 34, line 3-5; "tet ON/OFF").

Elbashir (EMBO): for the proposition that siRNA are valuable reagents for inactivation of gene expression in mammalian cells. However, Elbashir (EMBO) is silent as to the other elements of the claims.

Elbashir (Nature): for the proposition that siRNA are agents useful for mediating gene silencing. Again, however, Elbashir (Nature) is silent as to the other elements of the claims.

Deuschle: for the proposition that externally controllable systems of gene expression having both a DNA binding domain and a repressor domain are known. However, Deuschle is silent as to controlling the expression of siRNA and teaches controlled expression only in the context of a pol II promoter, ***not*** a pol III promoter.

Verma: for the proposition that lentiviral vectors are known to be useful for expressing antisense nucleic acids and ribozymes. However, Verma is silent as to siRNA, an entirely different class of molecules from antisense and ribozymes, and controlled expression.

From the foregoing it can be seen that the rejection is facially inadequate from a *prima facie* obviousness standpoint. First and foremost, the primary reference, Giordano, fails to teach the special type of controlled expression involving the use of both a DNA binding domain and a repressor domain. Indeed, this reference teaches the use of one having only a DNA binding domain. Deuschle is the only reference cited as teaching such a control element. However, Deuschle is silent on the use of such a control element in the context of siRNA and instead employs the control element in the context of "genes". Moreover, Deuschle is silent on the use of such a control element in the context of a pol III promoter. Indeed, Deuschle implicitly instructs the reader to use the control element only in the context of the very different pol II promoter, the CMV promoter.

We contend that the Examiner has failed to provide, or adequately provide, an "apparent reason" why one of skill would seek to use the pol II controllable expression system of Deuchle in the pol III siRNA construct of Giordano. *KSR Int'l Co. v. Teleflex, Inc.*, No. 04-1350 (U.S. Apr. 30, 2007). It appears from the Answer that the Examiner simply states the Deuschle

discloses "a novel way to regulate gene expression in higher mammalian cells and also offers unique possibility of reversibly down regulating the expression of cellular genes on top of normal cellular regulation." Answer, paragraph bridging pages 14-15. These comments go only to what the Examiner contends Deuschle brings to the party, so to speak, but says nothing in a cogent manner as to ***why*** one of skill would desire combine this work of Deuschle (which, again, is silent both as to siRNA and workability with pol III promoters) with teachings such as Giordano that relate to the controlled expression of siRNA, where Giordano already discloses the use of a different controlled expression system.

Moreover, the Examiner's statements regarding the motivation that is said to arise from Deuschle is telling, in that the Examiner himself recognizes that the combination of the technology with siRNA technology would offers a "unique possibility" and a "novel way to regulate" genes. This sounds strikingly like a recognition that a unique, novel and indeed exciting invention has indeed been made! If the realization of "unique" and "novel" combinations for further experimentation are a proper basis for finding an apparent reason for the combination, then indeed no non-obvious combination of elements could ever be made. This cannot be the law.

Lastly, the Board will recall the Appellants argued in their opening brief that the Examiner had not indicated on this record that there was a reasonable expectation that combining the Deuschle pol II related gene control expression system would be successful in controlling ***i) siRNA expression*** from ***ii) a pol III promoter***. Brief at 15. The Examiner has now sought to rectify this shortcoming by the comments at page 15 of the Answer, which we will reproduce here:

> One of ordinary skill in the art would have expected success in producing a polynucleotide construct comprising an externally controllable pol III promotor and a region encoding a siRNA wherein expression of the siRNA is regulated by a polypeptide regulator having a DNA binding domain and a repressor domain because ***all of the individual elements required by the claimed construct are*** [sic] ***were known and used successfully in the prior art.*** Giordano et al. teach the use of retroviral vectors to express siRNA under control of an externally controllable pol III promotor, Verma et al teach lentiviral vectors are a type of retroviral vector that have been successfully used to express heterologous nucleic acid sequences and Deuschle et al. teach successful use of the TetR-KRAB operator/repressor system to provide the possibility of reversibly down regulating the expression of cellular genes on top of their normal cellular regulation.

Answer at 15 (emphasis ours).

We fail to see how the foregoing statement, which simply restates what each reference is purported to teach, provides any reasonable expectation that using Deuschle pol II related gene control expression system could be successfully used to control siRNA expression from a pol III promoter. The fact that "all of the individual elements required by the claimed construct are [sic] were known and used successfully in the prior art" says absolutely nothing about whether the two elements would have worked "when combined" – we here have no reasoning as to why one of skill would expect that TetR-KRAB would work with siRNA as opposed to a gene, and we have no reasoning as to how or whether tetR-KRAB could work with an pol III promoter instead of a pol II promoter in the context of siRNA expression!

Claims 46 and 47

Claims 46 and 47, directed to transgenic stem cells and oocytes, are even further removed from the prior art. While the Examiner has for the first time in his Answer identified an on-the-side reference to "gametes" and "stem cells" in the Giordano reference, we nevertheless observe again that the Deuschle reference says nothing about gametes or stem cells so we know nothing about the ability of the TetR-KRAB construct to function in those cells, or the ability of such a

construct to function in those cells to regulate siRNA from a pol III promoter – indeed, the TetRKRAB in Deuschle is studied only in the context of HeLa cells (a human tumor cell line) looking at luciferase gene expression from a pol II ("CMV") promoter. We can find no discussion from the Examiner addressing these important separate issues. So, here, in the absence of some evidence or reasoning as to why one would expect the combination to function in stem cells or oocytes, there clearly is no proper *prima facie* obviousness rejection as to claims 46 and/or 47.

ii) Mammalian Cell Section 101 Rejection

With regard to the rejection of claim 41 on the section 101 concerns, we continue to maintain that just as a claim to a windshield wiper does not cover an entire car, or a claim to a "ring" does not "cover" a human wearing such a ring, that a claim to a cell is not directed to and does not "cover" a whole human, it covers only an infringing cell within the human. See, *e.g.*, *King Instruments Corp. v. Perego*, 65 F.3d 941, 956 (Fed. Cir. 1995) (holding that a claim direct to a component of an entire machine does not cover the entire machine). Such a claim may well cover a cell in the future that has been ***placed into*** a human, but it does not ***cover*** the human. In order to "cover" the human, the claims would be required to read "a human comprising the cell of claim 41" or something of that nature. This type of claim is not at issue here.

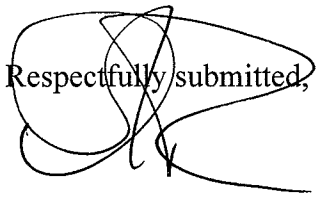
The subject matter of claims 46 and 47 are even further removed. These claims concern specifically genetically engineered stem cells and oocytes, respectively. There is no way that Appellants are aware, or that the Examiner has explained, that a human can be made out of stem cells or oocyte cells. While a human might have such cells in his or her body, but not be made entirely of such cells. Furthermore, these claims are also directed to "cells" and not to "humans comprising" such cells.

Furthermore, we are unaware of any rule or decision that supports the Examiner's rejection, and the Examiner has failed to refer us to any such rule or decision.

Conclusion

In summary, the Examiner has failed to demonstrate on the record that a proper prima facie obviousness rejection has been made with respect to the claims as argued in the opening brief and outlined above. The same can be said for the section 101 rejection. Thus, we contend that all of the rejections that still remain should should be reversed.

For the foregoing reasons, Appellants respectfully request that the Board reverse the rejections of all claims.



Respectfully submitted,

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Date: May 7, 2007